RISK FACTORS IN OVARIAN CANCER

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Summary: For 50 years, the three- and five-year survival rates of under 40% for invasive ovarian cancer in the USA have not significantly changed. Identifying those women who have a greater probability of developing the disease should contribute to improving survival. Our 3-year case-control study of 298 women from the metropolitan Washington, DC, area with primary epithelial ovarian cancer revealed a woman is at greater risk of developing ovarian cancer if she has a family history of the disease, experiences difficulty becoming pregnant, and has a normal menopause with hot flashes. Her risk for the disease is diminished with multiparity, a history of dysmenorrhea, and hysterectomy. Physicians should consider these risk factors when performing pelvic examinations in women and coordinate them with known changes in ovarian size and procedures to view the ovaries which may permit earlier recognition of ovarian cancer.

INTRODUCTION

The diagnosis of ovarian cancer in late stages, failure of treatment of advanced disease, and the poor survival rate have contributed to an increased interest in identifying those factors which might influence a woman's possibility of developing or of preventing ovarian cancer ([1-3]). Also, the National Cancer Institute in their monograph "Cancer control objectives for the nation: 1985-2000" state pelvic examination for ovarian tumors is unproven as a screening technique ([4]).

Laboratory and radiologic procedures to aid in the earlier diagnosis of ovarian

Supported by Contract NIH-NC1-NO1-CP-81051.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as representing the views of the Department of the Army or the Department of Defense.

cancer used most efficiently must be applied in women most and least likely to develop the disease. Ovarian epithelial tumors of low malignant potential are distinguished by criteria which separate them from the infiltrative growth pattern of carcinoma. Although tumors of low malignant potential and invasive carcinomas are recognized as distinct entities today, there is a suggestion of a continuum of epithelial changes from low malignant potential to invasive tumors ([3]). This study attempts to further define the woman at increased or reduced risk for ovarian cancer as well as to possibly identify differences between risk factors in women with tumors of low malignant potential as opposed to women with invasive ovarian cancers of the epithelial cell type.

MATERIAL AND METHODS

We attempted to identify all women age 20-79 residing in the Washington, DC, metropolitan area who were first diagnosed with primary epithelial ovarian cancer during the period August 1, 1978, to June 30, 1981. The discharge lists, tumor registries, or pathology departments of all of the 33 area hospitals in the District of Columbia, Maryland, and Virginia that treated ovarian cancer were regularly checked. Cases included women with tumors of low malignant potential as well as those with invasive ovarian cancers.

Controls were identified from hospital discharge lists and were matched to study cases according to age, race, and hospital of discharge. A woman was not eligible to be a control if her discharge diagnosis was potentially related to the exposures under study. Discharge diagnoses excluded were: breast disease, myocardial infarction, stroke, thromboembolism, gallbladder disease, osteoporosis, gynecologic complaints, melanoma and colon cancer. We also excluded women with psychiatric diagnoses.

For each identified case and control, we contacted the woman's physician to obtain permission to approach the patient for an interview. We also determined from physicians' records and the women themselves that control women had at least one ovary. Women who did not were excluded from the control group since they were not at risk for ovarian cancer. After physician consent, the study subject was interviewed at home as soon as possible and all within three months after hospital discharge.

We identified 400 women with histologically confirmed primary epithelial cancer of the ovary, of whom we interviewed 296 (74%). The remaining 104 women were not interviewed because of death (44), patient refusal (33) or incapacitation (12), physician refusal (8), loss of patient (3) or, move of patient from the area (4). We identified 439 controls (age 20-79), 343 (78%) of whom were interviewed. The remaining 96 were not interviewed because of patient refusal (50), death (13) or incapacitation (8), physician refusal (11), and other reasons (14).

The interview lasted about one hour and included questions about menstrual, sexual, reproductive, medical, and occupational histories and exposure to drugs, alcohol, and tobacco. We also asked for the names and addresses of the subjects' gynecologists, surgeons, and hospitals, from whom we sought confirmation and additional data on medical history. We obtained the patient's written approval and collected all pertinent medical records and representative microscopic slides for each case. All pathologic slides were reviewed by one of the authors (HJN).

All cases underwent an abdominal surgical procedure. Verification of each case was accomplished by a reading of current and past medical records, including history and physical examination, operative report, pathology and cytopathology reports, diagnostic roentgenographic studies, discharge summary, and evaluation of the spread of the disease. If this information suggested a possibility that the cancer did not arise primarily in the ovary, the case was not included in the study. We can not find a larger study reported of primary epithelial ovarian cancer using the same methods of case and control selection as previously mentioned.

Two hundred forty-five (83%) of the cases were diagnosed as invasive carcinoma and the remaining 51 cases (17%) as epithelial tumor of low malignant potential. The average age for all patients was 54 years. Women with invasive carcinoma had an average age of 57 years, whereas those with low malignant potential tumors were considerably younger (average age, 44). Eighty-nine percent of the cases were white and the remainder, black.

The effect of each factor on the risk of tumors of low malignant potential and of invasive carcinoma was estimated. The measure of effect was the estimated rate ratio (RR), the ratio of disease incidence in the exposed group to that in the unexposed. A RR of 2.0 for tumors of low malignant potential, for example, indicates that the incidence of it is twice as great among exposed women as among unexposed; conversely, a rate ratio of 0.5 indicates that

the incidence is half as great compared with unexposed individuals. The difference between the effect of an exposure on tumors of low malignant potential risk and risk for invasive carcinoma was tested for statistical significance. The estimated effects were adjusted for the effects of confounding variables by logistic regression modelling ([5]). The effects of an exposure on low malignant potential risk and invasive ovarian cancer risk were modelled as a multinominal logistic function following the method described by Jones ([6]).

RESULTS

Women who had difficulty getting pregnant faced a higher risk of low malignant potential tumors (RR, 2.3) than of invasive carcinoma (RR, 1.2) as show in table 1. This was the strongest difference between low malignant tumors and invasive carcinoma, but the difference could be ascribed to chance ($P = .12$). A family history of ovarian cancer increased the risk of incasive carcinoma (RR, 2.8) but did not affect low malignant potential tumor risk. There was only one woman with a family history of tumors of low malignant potential. Menopausal hot flashes increased the risk for invasive carcinoma (RR, 1.6). Also, women with menopause, not induced by bilateral oophorectomy (natural) had an increased risk for tumors of low malignant potential (RR, 1.9) (table 1).

A reduced risk for both invasive carcinoma and low malignant tumors was noted in women who had given birth to several children, a reduction particularly evident for invasive carcinoma (RR, .6) (table 1). In addition, the risk for both ovarian neoplasms was reduced in women who had had menopause induced by hysterectomy (RR, 0.6, 0.7) or who had experienced dysmenorrhea (RR, 0.4, 0.6) or used estrogens during menopause (RR, 0.3, 0.6) (table 1). A history of severe menstrual cramps was commonly associated with a reduced risk for low malignant potential tumors (RR, 0.5). Although the number of women in each group is small, there was a reduced risk for both ovarian neoplasms in women who had used oral contraceptives of any type, dose or duration within 12 months of diagnosis. For women who had used oral contraceptives at any other time of life there was no statistical difference between the low malignant potential and invasive carcinoma cases or the control group (tab. 1).

DISCUSSION

The risk factors studied were similar for women with ovarian epithelial tumors of low malignant potential and for those with invasive ovarian cancers. No factor comparing women in the two groups had a P value $< .05$. The strongest difference between the two neoplasms was that women who had trouble getting pregnant and those with a natural menopause were at greater risk to develop low malignant potential tumors. A family history of ovarian cancer was more associated with the development of invasive carcinoma than of a low malignant potential tumor. Women who recalled having severe menstrual cramps appeared to be at lower risk to develop low malignant potential tumors than invasive carcinoma.

Both the younger premenopausal woman with a low malignant potential tumor and the older postmenopausal woman with invasive carcinoma require surgical extirpation of the neoplasm to the degree allowed by the extent of the disease and condition of the patient. After initial surgery, a conservative therapeutic approach is indicated for the less biologically aggressive low malignant potential tumors ([7]) whereas more vigorous measures are recommended for invasive carcinoma. Usually the survival in women with low malignant potential tumors is good, whereas that of women with invasive carcinoma is poor ([3, 7]). Nonetheless, the similarities of the risk factors we stu-

Table 1. – *Estimated Rate Ratios and Confidence Limits for Low Malignant Potential and Invasive Ovarian Cancers.*

	Controls	Low Malignant Potential			Invasive Ovarian Cancer		
		No.	RR	95% Confidence Limits	No.	RR	95% Confidence Limits
Parity							
0	80	18	1.0		71	1.0	
1 - 2	133	24	1.0	.46-2.08	101	0.7	.47-1.13
3+	119	10	0.8	.30-1.94	72	0.6	.34-.89
Menstrual Cramps - Severe							
No	226	40	1.0		177	1.0	
Yes	90	10	0.5	.23-1.12	65	0.9	.65-1.39
Family History Ovarian Cancer							
No	326	51	1.0		232	1.0	
Yes	6	1	1.2	.13-12.1	12	2.8	1.03-7.70
Infertility							
Never tried or no problem	257	35	1.0		184	1.0	
Had trouble getting pregnant	62	15	2.3	1.10-4.82	53	1.2	.77-1.82
Oral Contraceptives							
Never used	253	28	1.0		191	1.0	
Used within 12 months	13	3	0.3	.06-1.53	4	0.6	.18-2.28
Former used	65	21	1.2	.51-2-70	46	1.2	.71-2.02
Menopause							
Premenopausal	86	32	1.0		60	1.0	
Not induced by hysterectomy	165	17	1.9	.42-9.00	144	0.8	.38-1.50
Hysterectomy induced	79	3	0.6	.14-2.93	39	0.7	.36-1.42
Menopausal Cramps							
No	258	49	1.0		211	1.0	
Yes	61	2	0.4	.07-1.94	29	0.6	.32-.97
Menopausal Flashes							
No	229	41	1.0		150	1.0	
Yes	90	10	1.4	.50-3.81	91	1.6	1.03-2.47
Menopausal Estrogens							
No	224	48	1.0		183	1.0	
Yes	108	4	0.3	.11-1.08	61	0.6	.40-.91

The estimated effects of parity, menstrual cramps, family history, infertility and oral contraceptive use were adjusted for each other and for the effects of age and race. The estimated effects of the other factors in the table were adjusted for each other and for the effects of age and race.

died suggest that low malignant potential tumors and invasive carcinoma are very close in most respects. Therefore, women with the two cells types together form a more robust study of risk factors for ovarian cancer.

It has been reported that the use of oral contraceptives significantly reduces the risk of ovarian cancer ([8-10]). Our data do not support this finding. Among women who had used oral contraceptives of any type, dose or duration prior to one year

before diagnosis there was no difference between women who had ovarian cancer or the control group. There appeared to be a reduced risk of ovarian cancer in women who had used oral contraceptives within 12 months of diagnosis. However, the number of cases is small and the differences between the two could therefore easily be due to chance. Even if the observations are meaningful, the risk of giving oral contraceptives to women over the age of 40 to reduce the occurrence of ovarian cancer would appear to outweigh the benefit. Differences in our data and those reports suggesting oral contraceptives protect against ovarian cancer possibly relate to our selection of cases and controls.

The woman at risk to develop an ovarian cancer tends to have a history of difficulty in conceiving, is inclined to be in a family in which ovarian cancer has previously occurred, and will experience menopausal hot flashes and a natural menopause. A woman is at a reduced risk for ovarian cancer if she has given birth to several children, has experienced painful menstrual and menopausal cramps, has had menopause induced by hysterectomy, and possibly, has used estrogens around the menopause. Perhaps applying these risk factors along with known changes in ovarian size during pelvic examination could select those women who might be further monitored by established techniques to visualize the ovaries. Of course, perimenopausal or postmenopausal women with enlarged ovaries should have them removed. Thus, women who typically display no symptoms of ovarian cancer may be detected with a potential to reduce their mortality.

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